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NEPHROLOGY FORUM

Renal neural activity in hepatorenal syndrome

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Case presentation

A 61-year-old white man was admitted to the Iowa City Veterans Administration Medical Center for increasing abdominal girth and swelling of the legs over 2 weeks; he also noticed darkening of his urine as well as yellow skin and eyes. The patient, known to be a chronic alcoholic, had had multiple previous admissions for treatment of alcohol withdrawal. He smoked cigarettes and had mild chronic obstructive pulmonary disease. He was not taking medications.

Physical examination disclosed a slightly confused icteric man. Blood pressure was 125/75 mm Hg recumbent and 120/70 mm Hg standing; radial pulse was 84 beats/min recumbent and 92 beats/min standing; oral temperature was 36.9°C; respirations were 14/min. The sclerae and skin were icteric, and bilateral Dupuytren's contractures were present; also evident were multiple telangiectases over the upper trunk, neck, and face and a caput medusae with reversal of flow in dilated superficial abdominal wall veins. The patient had marked ascites and pitting edema of the legs below the knees. He was slightly confused and was disoriented as to time and place. A fine tremor of the outstretched hands was present, and the patient had an unsteady gait; asterixis was not present.

On admission laboratory data revealed a normal complete blood count, prolonged prothrombin time, and a normal urinalysis. The serum sodium was 133 mEq/liter; potassium, 3.7 mEq/liter; chloride, 97 mEq/liter; bicarbonate, 25 mEq/liter; BUN, 2 mg/dl; creatinine, 0.8 mg/dl; total bilirubin, 5.7 mg/dl; albumin, 2.1 g/dl; SGOT, 203 mU/ml; SGPT, 73 mU/ml; alkaline phosphatase, 480 mU/ml; and cholesterol, 112 mg/dl. Radiographs of the chest and abdomen disclosed a normal heart, normal lungs, an old fracture of the left ninth rib, and ascites; gallstones were not seen. Ultrasound examination of the hepatobiliary system was normal. A 20 ml diagnostic paracentesis revealed the ascitic fluid to be a transudate without evidence of infection.

The patient was treated with a high-carbohydrate, low-protein, and low-sodium diet, supplemented with multivitamins and low doses of lactulose and chlordiazepoxide. Oral fluids were limited, and spironolactone therapy was begun. Over the next week the patient remained confused and lethargic; a CT scan of the head and a lumbar puncture were normal. Insidious oliguria ensued. The body weight did not change, and the serum creatinine concentration rose slowly to a zenith of 7.0 mg/dl; serum bicarbonate concentration decreased to a nadir of 13 mEq/liter concurrent with an increase in the serum chloride concentration to a peak of 117 mEq/liter; serum sodium and potassium concentrations remained relatively normal. Urine sodium concentrations, determined serially, were always less than 10 mEq/liter; the fractional sodium excretion was uniformly less than 0.30% and urinary osmolality was greater than 360 mOsm/kg H_2O. Cautious attempts were made at combined intravascular volume expansion using albumin and diuretic therapy using furosemide, with the patient under central cardiovascular pressure monitoring (the basal mean pulmonary artery capillary wedge pressure was 12 mm Hg); these attempts were to no avail. The patient developed bilateral pneumonia with progressive hypoxemia, and he died on the 21st hospital day. Autopsy disclosed severe alcoholic cirrhosis with portal hypertension as manifested by ascites and splenomegaly. The kidneys were normal. The lungs showed bilateral pneumonia due to *Staphylococcus aureus* and *Escherichia coli*.

Discussion

DR. GERALD F. DIBONA (*Professor and Vice Chairman, Department of Internal Medicine, University of Iowa College of Medicine, and Chief, Medical Service, Veterans Administration Medical Center, Iowa City, Iowa*): The clinical characteristics of this patient's illness and hospital course fit the general description of the hepatorenal syndrome. He had unexplained progressive renal failure in the presence of hepatic disease; neither clinical, laboratory, nor anatomic evidence of other known causes of renal failure could be found [1, 2].

Strong circumstantial evidence indicates that the renal failure in hepatorenal syndrome is functional in nature. Despite markedly abnormal renal function, the histology of the kidney is usually normal or only mildly abnormal. Tubular functional integrity is well maintained, as reflected by persistent avid sodium reabsorption and relatively unimpaired concentrating ability. Direct evidence of the functional nature of the renal failure is derived from the demonstration that kidneys transplanted from patients with the hepatorenal syndrome are capable of resuming normal function in recipients [3].

Patients with advanced cirrhosis of the liver often display a characteristic circulatory disorder; these individuals tend to develop arterial hypotension and to avidly retain sodium. Thus, these patients generally manifest edema and ascites. These are also the clinical characteristics of patients who develop the

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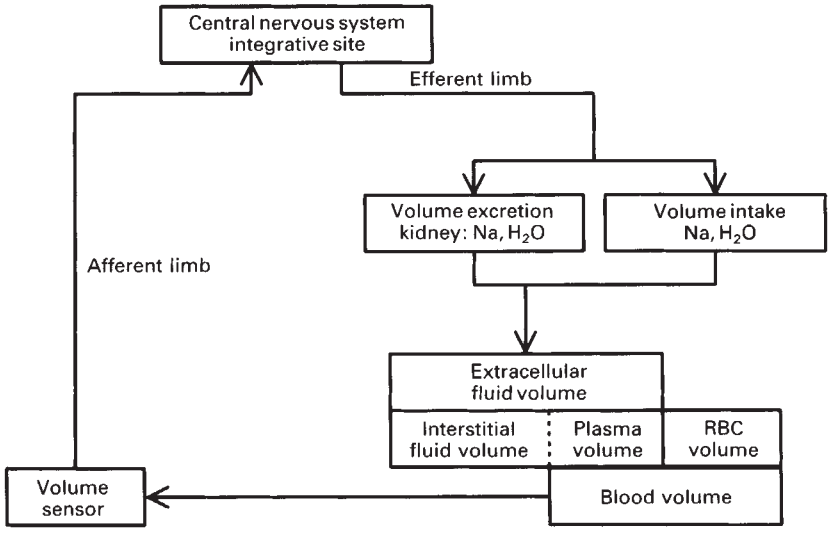

Fig. 1. *Pathways for the regulation of extracellular fluid, plasma, and blood volume by a reflex mechanism involving the autonomic nervous system.*

hepatorenal syndrome. In a recent review of abnormal volume homeostasis in patients with cirrhosis, Better and Schrier expressed the view that "patients with hepatorenal syndrome merely represent the extreme spectrum of disturbance of volume control observed in all cirrhotic patients with ascites and renal sodium retention [4]." They reviewed the evidence in support of the "underfilling" (a decrease in effective blood volume with secondary renal sodium retention) and "overflow" (primary renal sodium retention) theories of sodium retention and ascites, and concluded that neither theory alone adequately explains the findings in patients with cirrhosis. The authors proposed that both underfilling and overflow are involved in cirrhotic ascites. Alternately, each of the proposed mechanisms might be more prominent at different stages in the course of the disease [5]. Levy has postulated that the early phase of the disease is characterized by primary sodium retention, which progresses to ascites formation and a tendency toward arterial hypovolemia that is related to alterations in the forces regulating transcapillary fluid partitioning, splanchnic venous pooling, and peripheral vasodilation. The later phase of the disease might be characterized by a decrease in effective blood volume with secondary renal sodium retention. Although the role of increased renal sympathetic nerve activity as an efferent arm of the mechanism of renal sodium retention has been often discussed [2], Better and Schrier hypothesized that both the overflow and underfilling theories involve specific stimuli that elicit increased efferent renal sympathetic nerve activity (ERSNA) which, in turn, plays a major role in the renal sodium retention [4]. In recent years, a greater understanding of both the nature and distribution of the intrinsic renal innervation and the complexity of factors controlling ERSNA has led to a burgeoning interest in the neural control of renal function [6].

Neural control of effective blood volume

According to the underfilling theory, a decrease in effective blood volume is the stimulus that sets in motion a sequence of events that tends to restore the effective blood volume to a normal level. The concept of a neural mechanism controlling blood volume parallels that of a classic neural reflex arc. That is, the mechanism involves an afferent limb consisting of a sensor that continuously monitors the blood volume, and an afferent neural pathway that conveys information from the sensor to an integrative site in the central nervous system. From this integrative site emerges an efferent limb consisting of neurohumoral pathways; stimuli from this limb influence the function of effector organs that ultimately produce the appropriate change in the blood volume.

This concept of neural volume control, first proposed by Gauer and Henry [7], is presented in Figure 1. Their concept of reflex volume regulation has three requirements: (*1*) a well-defined compliance of the low-pressure vascular system relating intravascular volume to filling pressure; (*2*) appropriate receptor (sensor) networks in the walls of the low-pressure system that are responsive to changes in wall tension and that discharge in appropriate areas of the central nervous system; and (*3*) related efferent neurohumoral mechanisms that control the major regulators of plasma volume: thirst, renal excretion of water and sodium, and distribution of the extracellular fluid.

Several investigators have studied compliance (defined as the quotient blood volume/central venous pressure x kg body weight) and have identified a narrow and well-defined range of effective vascular compliance and intrathoracic vascular compliance in humans under various experimental conditions; the values are 1.7 to 3.5 and 0.9 to 1.2 ml/mm Hg/kg body weight, respectively [reviewed in 7]. Because of the large differences in the intrathoracic and extrathoracic blood volumes and the relative similarity of their vascular compliances, the distensibility of the intrathoracic compartment must be much greater than that of the extrathoracic compartment. Receptors in the walls of the intrathoracic system are ideally suited for the detection of changes in blood volume; the atria are the most distensible part of this system. Mechanoreceptors (unencapsulated neural elements) are present in the wall of the left atrium; these discharge with atrial filling and respond to changes in atrial transmural pressure (Paintal type B receptor) [8]. The mechanoreceptors discharge into afferent myelinated fibers in the vagus nerve [9], which have central representation in both the medulla [10] and the supraoptic and paraventricular nuclei of the hypothalamus

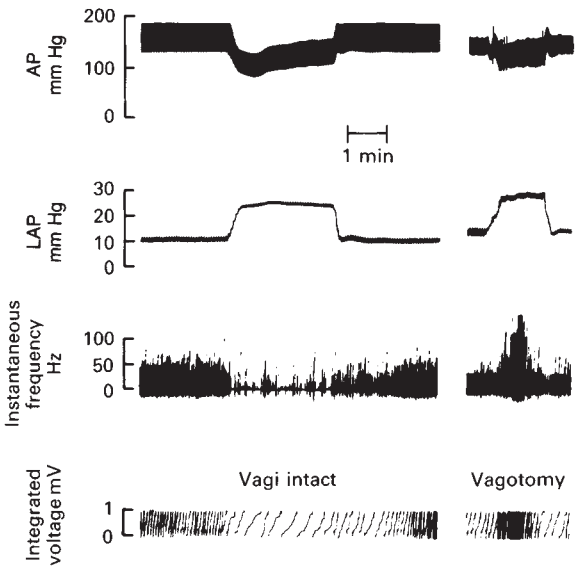

Fig. 2. *Effect of left atrial balloon inflation on arterial pressure (AP), left atrial pressure (LAP), the instantaneous frequency and integrated voltage of efferent renal sympathetic nerve activity in anesthetized dogs with vagi intact* (left panel), *and after bilateral cervical vagotomy* (right panel).

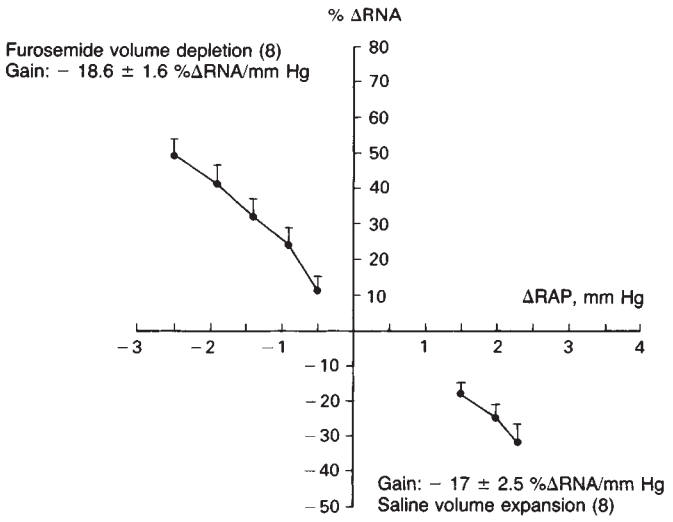

Fig. 3. *Effect of volume expansion (isotonic saline loading) and volume depletion (furosemide administration) on the relationship between the change in right atrial pressure (ΔRAP) and the change in renal nerve activity (% ΔRNA) in conscious rats.* Gain = %ΔRNA/ΔRAP.

[11]. Thus, the left atrial mechanoreceptor fulfills the requirements for a sensor located in the low-pressure vascular system: it possesses a well-defined compliance relating intrathoracic volume to filling pressure, and it responds to changes in wall tension (stretch) by discharging into afferent vagal fibers that have appropriate central nervous system representation.

The related efferent neurohumoral effector mechanisms depend on an integrated response of the central nervous system centers. Left atrial mechanoreceptor stimulation (increases in left atrial pressure due to blood volume expansion or left atrial balloon inflation) produces four consequences: (*1*) It elicits discharge of the supraoptic and paraventricular nuclei. These same nuclei are also sensitive to osmotic stimuli, and they provide a neurophysiologic basis for the interaction of volume and osmotic stimuli, a mechanism that regulates release of antidiuretic hormone [11]. (*2*) It decreases arterial plasma concentration of antidiuretic hormone [12]. (*3*) It alters sympathetic outflow to the pre- and postcapillary peripheral resistance vessels, a change resulting in an altered filtration pressure which, in turn, favors the movement of fluid from blood to the interstitial space [13]. (*4*) Finally, it decreases ERSNA [14, 15] (Fig. 2).

When left atrial pressure is increased by left atrial balloon inflation, arterial pressure decreases, partly because of obstruction of filling of the left ventricle and reduced cardiac output. Ordinarily, a decrease in arterial pressure elicits a reflex increase in ERSNA mediated by carotid and aortic baroreceptors. However, the abrupt and sustained decrease in ERSNA reflects the dominant influence of the left atrial mechanoreceptors. After vagotomy, which interrupts the afferent limb of the reflex arc, an increase in left atrial pressure and decrease in arterial pressure are associated with an increase in ERSNA that relationships, which correspond to the gain of the system, are similar [16].

is derived from the carotid baroreceptor. The decrease in ERSNA by left atrial mechanoreceptor stimulation is known to be specific for the kidney because simultaneously measured cardiac sympathetic nerve activity increases, and neither lumbar nor splenic sympathetic nerve activity change [14]. Using differential cooling of the vagus and small left atrial balloons which, on inflation, do not affect left ventricular filling or arterial pressure, Linden, Mary, and Weatherill found the decreased ERSNA response to depend on left atrial receptors discharging into myelinated vagal afferent fibers [9]. Several groups have demonstrated that expansion of blood volume decreases, and depletion of blood volume increases, ERSNA in animals in which carotid and aortic baroreceptor afferent input is either eliminated or held constant, and that the changes in ERSNA correlate inversely with the changes produced in left atrial pressure [6]. Thus, left atrial mechanoreceptor stimulation, as occurs with increases in left atrial pressure produced by volume expansion, elicits an integrated neurohumoral response consisting of a reduction in plasma concentration of antidiuretic hormone, enhanced filtration of fluid from blood to the interstitial fluid volume compartment, and a reduction in ERSNA.

In this context, the underfilling theory envisions a decrease in effective blood volume, a corresponding decrease in left atrial pressure, and an unloading of the left atrial mechanoreceptors. Although there is some hysteresis, the left atrial mechanoreceptor mechanism operates in a bidirectional fashion: as might be predicted from what I have just said, the integrated neurohumoral response to reduced left atrial pressure consists of an increase in plasma concentration of antidiuretic hormone, decreased filtration of fluid from blood to the interstitial fluid volume compartment, and an increase in ERSNA. In studies using renal nerve recording techniques in conscious, freely moving rats, we demonstrated that volume expansion both increases right atrial pressure, which in rats closely correlates with left atrial pressure, and decreases ERSNA, whereas volume depletion with furosemide decreases right atrial pressure and increases ERSNA (Fig. 3); the slopes of the two

Disturbances of neural control of effective blood volume in cirrhosis

According to the overflow theory as applied to patients with cirrhosis, the stimulus for increased ERSNA is an increase in intrahepatic sinusoidal pressure [4]. This suggestion is based on the observation that renal sodium retention and ascites formation are abolished and normal mineralocorticoid escape is restored in experimental biliary cirrhosis when the elevated intrahepatic sinusoidal pressure characteristic of this condition is relieved by a side-to-side portacaval shunt [17]. Other workers have studied the effect on renal function of alterations in pressure within various segments of the hepatic portal circulation. Haberich and coworkers observed a rapid reduction in urine flow following either brief or prolonged increases in portal vein pressure in the rat; conversely, decreasing portal vein pressure produced an increase in urine flow [18, 19]. They produced changes in portal vein pressure using an inflatable cuff to occlude the main portal vein. Liang showed that increases in portal vein pressure of less than 15 cm H_2O, produced by occluding the main hepatic portal vein in the dog, increased urinary flow rate and chloride excretion as well as renal plasma flow and glomerular filtration rate [20]. Occluding the main hepatic portal vein would tend to decrease intrahepatic sinusoidal pressure. These responses were reversibly abolished by application of local anesthetics to the renal neurovascular pedicle but not by vagotomy. This study suggests that increasing portal vein pressure without increasing intrahepatic sinusoidal pressure decreases ERSNA. In confirmation of this view, Niijima observed that 5-minute periods of main portal vein occlusion in the rabbit produced decreases in mean arterial pressure and ERSNA that were unaffected by vagotomy [21]. We showed that main portal vein occlusion in the dog produced a 40% decrease in ERSNA, from 9.8 ± 0.5 to 7.4 ± 0.4 Hz, as well as a slight reduction in mean arterial pressure (Fig. 4). Again, these decreases in ERSNA occurred with decreases in mean arterial pressure that ordinarily would lead to sinoaortic baroreceptor-mediated increases in ERSNA.

In contrast to these results, Anderson et al showed that acute increases in portal vein pressure produced by partial main portal vein occlusion in dogs decreases cardiac output and mean arterial pressure [22]. Further, despite a constant renal arterial pressure, they found that renal blood flow, glomerular filtration rate, urinary solute excretion, and free-water clearance also decreased; renal vascular resistance and renin secretion increased. Renal denervation prevented decreases in renal blood flow, glomerular filtration rate, and urinary solute excretion as well as increases in renal vascular resistance and renin secretion rate, but it did not prevent antidiuresis. The investigators considered these observations to be compatible with a splanchnorenal neural reflex. To exclude the possibility that the renal responses were related to the decreases in mean arterial pressure and cardiac output, they partially occluded the thoracic inferior vena cava (TIVC) in an additional group of dogs, thus producing reductions in mean arterial pressure and cardiac output similar to those occurring with main portal vein occlusion. Although they observed no changes in renal blood flow, glomerular filtration rate, and renal vascular resistance at constant renal arterial pressure, the level of portal venous pressure achieved with partial TIVC occlusion (9 mm Hg) was much less than that achieved with main portal vein occlusion

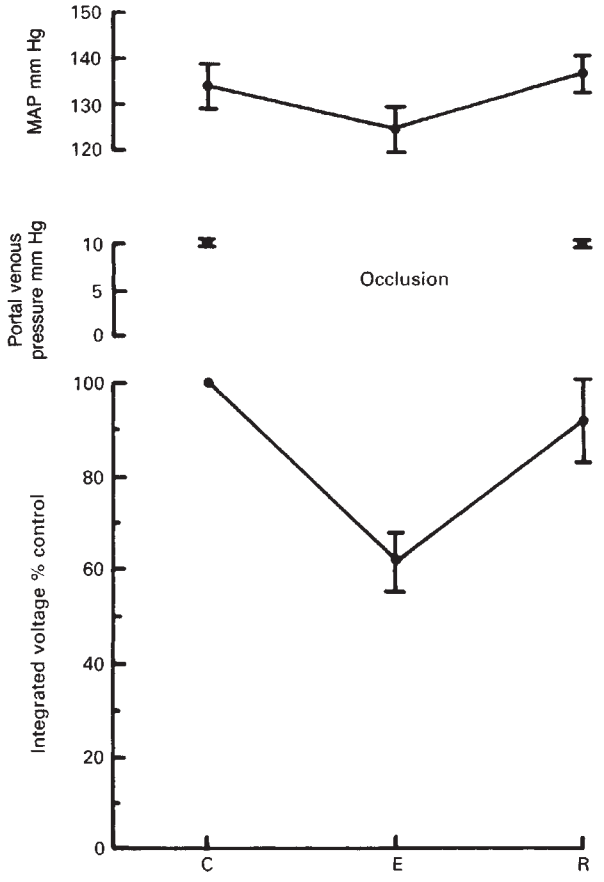

Fig. 4. *Effect of main portal vein occlusion on mean arterial pressure and integrated voltage of efferent renal sympathetic nerve activity in anesthetized dogs.*

(20 mm Hg). Unfortunately, data on left atrial pressure, the stimulus for the left atrial mechanoreceptors that are known to be a critical determinant of ERSNA, were not presented for either intervention. Decreases in urinary solute excretion and free-water clearance also were found with partial TIVC occlusion; we previously showed that these decreases depend on intact renal innervation [23]. In contrast to the previously mentioned studies by Liang [20] and Niijima [21], work by Anderson and colleagues suggests that an increase in portal vein pressure produces increases in ERSNA, even though data on renal nerve recordings were not presented [22].

Subsequent clarification of these conflicting results was derived from neurophysiologic studies. Niijima studied afferent hepatic nerve activity in the isolated perfused guinea pig liver and the rabbit liver in vivo [24]. He increased the perfusion pressure in the portal vein of the isolated guinea pig liver and raised the portal venous pressure by intravenous fluid injection in the rabbit in vivo. Both maneuvers, which probably increased intrahepatic sinusoidal pressure, increased afferent hepatic nerve activity. Increasing hepatic arterial pressure was without affect. Studies by Kostreva, Castaner, and Kampine in dogs provide the strongest evidence for a hepatorenal neural reflex arc, however [25]. Inferior vena cava occlusion at the diaphragm increased hepatic and portal venous pressure by about 5 to 30 mm Hg without affecting mean arterial pressure;

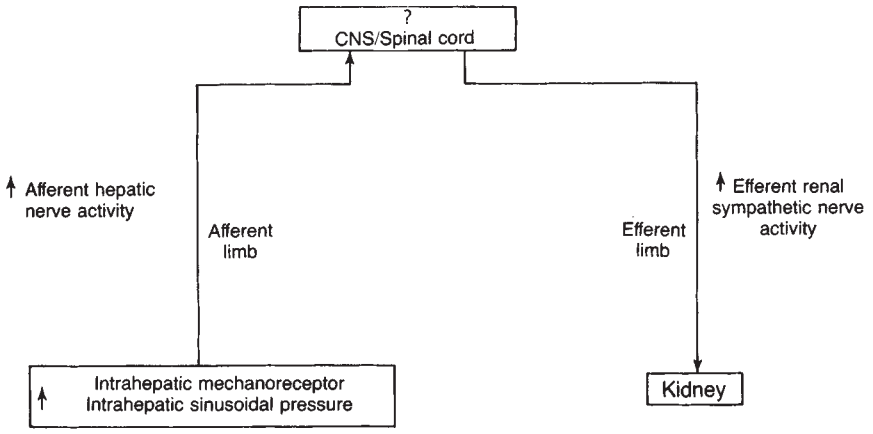

Fig. 5. *Pathways involved in the hepatorenal reflex.*

the occlusion also increased both hepatic afferent nerve activity and ERSNA. Hepatic nerve section prior to inferior vena cava occlusion abolished the increase in ERSNA. Neither carotid sinus denervation, bilateral vagotomy, nor phrenectomy produced an effect on the ERSNA response to inferior vena cava occlusion. Main portal vein occlusion, which increased portal venous but not hepatic venous pressure, either did not increase or slightly decreased ERSNA. Inferior vena cava occlusion at the diaphragm also increased cardiopulmonary sympathetic nerve activity (measured in ansa subclavia), but this maneuver was not associated with a change in heart rate or arterial pressure; hepatic nerve section reduced but did not abolish this response. This study localized the site of mechanoreceptors involved in a hepatorenal reflex arc to an intrahepatic sinusoidal site. This reflex arc is stimulated by increased intrahepatic sinusoidal pressure. Although increased portal venous pressure by itself decreases ERSNA, the combination of increased hepatic venous, portal venous and, therefore, intrahepatic sinusoidal pressure increases ERSNA. These observations further underscore the dominance of the intrahepatic sinusoidal pressure in an assessment of the effects of alterations in pressure in the hepatic portal circulation on ERSNA.

Patients with cirrhosis who have renal sodium retention, edema, and ascites uniformly manifest portal hypertension. Portal hypertension is defined as a direct portal vein pressure or wedged hepatic vein pressure of more than 5 mm Hg greater than the inferior vena cava pressure; we will infer that portal hypertension reflects increased intrahepatic sinusoidal pressure [26]. In patients with alcoholic cirrhosis, direct measurement of portal vein pressure correlates extremely well ($r = 0.96$, $N = 29$) with simultaneously determined wedged hepatic vein pressure over a range of 0 to 30 mm Hg [26]; these levels are similar to those shown by Kostreva et al to increase ERSNA [25]. Thus, in the presence of portal hypertension, one finds all the elements of a classic hepatorenal neural reflex arc (Fig. 5): an *afferent limb* consisting of intrahepatic baroreceptors that respond to an increase in intrahepatic sinusoidal pressure by eliciting increased afferent hepatic nerve activity, and an *efferent limb* consisting of increased ERSNA. Thus, with both the underfilling and overflow theories, neural reflex mechanisms elicit increases in ERSNA (Fig. 6), which serves as an effector pathway capable of influencing renal function.

Effects of ERSNA on renal function

The effects of the renal nerves on renal function are multiple and complex [6]. The intrinsic renal innervation is exclusively noradrenergic and involves the afferent and efferent arterioles, juxtaglomerular apparatus, proximal and distal convoluted tubules, and thick ascending limb of Henle's loop. Increases in ERSNA produce renal vasoconstriction; neither physiologic nor anatomic evidence supports the existence of sympathetic cholinergic vasodilator fibers in the kidney. Direct electrical stimulation of the efferent renal nerves produces frequency-dependent decreases in renal blood flow and glomerular filtration rate that are abolished by renal alpha-adrenoreceptor (alpha-1) or adrenergic blockade.

Direct as well as reflex alterations in ERSNA produce reciprocal changes in urinary sodium and water excretion without eliciting changes in glomerular filtration rate, renal blood flow, or intrarenal distribution of blood flow. This direct neural effect on renal tubular sodium reabsorption occurs in the proximal convoluted tubules, the thick ascending limb of the loop of Henle, and in the more distal nephron segments. Although increases in ERSNA are known to increase the renal secretion of renin and prostaglandins, the neural effect on renal tubular sodium reabsorption does not depend on the intermediate action of angiotensin II or prostaglandins [6]. Using a variety of alpha- and beta-adrenoreceptor antagonists, we have shown that the antinatriuretic response to renal nerve stimulation is mediated by renal alpha-1 adrenoreceptors, but that renal alpha-2, beta-1, and beta-2 adrenoreceptors are not involved [27]. Conversely, the renin secretory response to renal nerve stimulation is mediated by renal beta-1 adrenoreceptors; neither renal beta-2, alpha-1, nor alpha-2 adrenoreceptors (inhibitory or stimulatory) are involved [27].

The vital role of the efferent renal sympathetic nerves in the regulation of renal sodium handling is best shown in studies in unanesthetized animals and humans. Gill and Bartter demonstrated that normal subjects with autonomic insufficiency produced by guanethidine administration were unable to lower urinary sodium excretion sufficiently to avoid negative external sodium balance in response to a reduction in dietary sodium intake, despite decreases in glomerular filtration rate [28]. Patients with the Shy-Drager form of idiopathic autonomic

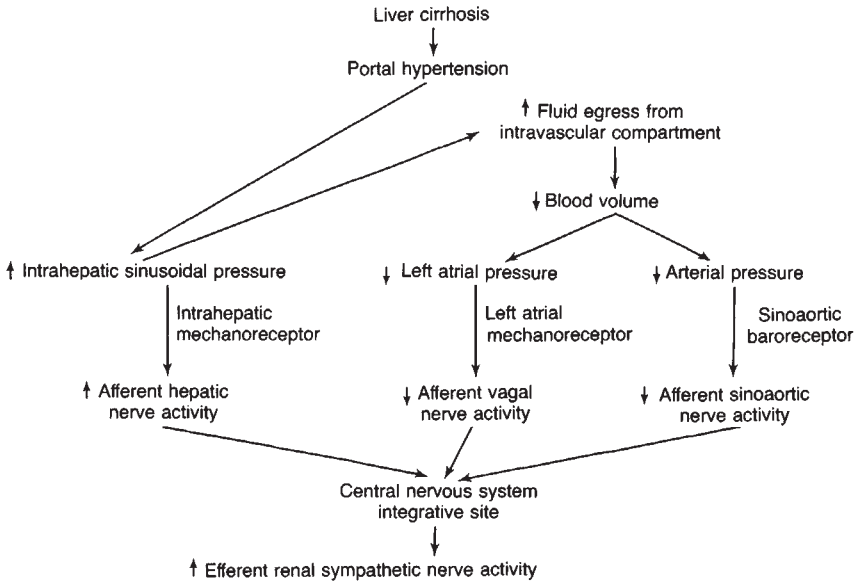

Fig. 6. *Pathways by which the underfilling theory* (right-hand portion) *and the overflow theory* (left-hand portion) *can account for an increase in efferent renal sympathetic nerve activity.*

insufficiency have a similar defect, even if they are receiving mineralocorticoid hormone [29]. Chronic bilateral renal denervation or systemic sympathetic blockade with reserpine or guanethidine renders conscious rabbits [30] and dogs [31] unable to reduce urinary sodium excretion sufficiently to avoid negative external sodium balance when challenged with a reduction in dietary sodium intake. We demonstrated that renal denervation renders the conscious rat unable to maintain external sodium balance when dietary sodium intake is restricted; negative external sodium balance occurred [32]. Thus, the efferent renal sympathetic nerves are an important component of the body's defense against sodium losses and therefore extracellular fluid volume depletion.

Evidence for increased ERSNA in cirrhosis

What evidence supports increased efferent renal sympathetic nerve activity in human subjects with hepatic cirrhosis, edema, and ascites? In cirrhotic patients with marked reduction in the renal clearance of para-aminohippurate (PAH) and inulin, intravenous administration of 50 g of albumin had little effect on the renal clearances of those substances [33]. However, the prior administration of albumin prevented a fall in mean arterial pressure when phenoxybenzamine, an alpha-adrenoreceptor antagonist, was subsequently administered intravenously; phenoxybenzamine increased the renal clearance of PAH more than twofold [33]. Epstein and coworkers noted that intrarenal infusion of phentolamine, an alpha-adrenoreceptor antagonist, did not increase renal blood flow (measured via the radioactive xenon washout technique) in cirrhotic patients [34]. But the majority of patients experienced significant reductions in arterial pressure that could have masked phentolamine-induced increases in renal blood flow. Henriksen and colleagues demonstrated that the concentration of norepinephrine in renal vein blood (mean, 0.79 ng/ml) exceeded that in simultaneously obtained arterial boood (mean, 0.59 ng/ml) in all 5 cirrhotic patients examined; no difference in epinephrine concentrations was observed [35]. In a subsequent report from the same laboratory, Ring-Larsen and associates reported that the concentration of norepinephrine in renal vein blood (mean ± SE, 0.63 ± 0.11 ng/ml) exceeded that in simultaneously obtained arterial blood (0.47 ± 0.09 ng/ml) in all 10 cirrhotic patients examined [36]. In addition, these studies demonstrated that peripheral plasma norepinephrine concentrations were higher in cirrhotic patients than in control subjects, and that this increase was not due to decreased hepatic extraction. The increased peripheral plasma norepinephrine concentrations correlated positively with measurements of wedged hepatic vein pressure ($r = -0.86$) and correlated negatively with measurements of plasma volume ($r = -0.83$); these results support both the overflow and underfilling theories.

Using the radioactive xenon washout technique, Ring-Larsen and associates showed that basal renal blood flow was lower, and renal vascular resistance higher, in cirrhotic patients than in control subjects [36]. During a 60° head-up tilt, renal vascular resistance and peripheral plasma norepinephrine concentration increased in parallel in the cirrhotic and control subjects [36]. The assessment of increased systemic or regional sympathoadrenergic activity is difficult when based on measurements of peripheral plasma norepinephrine concentrations alone [37–39], but considerable data are available to permit a reasonably accurate prediction of ERSNA from renal venoarterial plasma norepinephrine concentration differences or secretion rates. When ERSNA is zero in the denervated kidney, the concentration difference has a negative value; the plasma norepinephrine concentration in the renal vein blood is less than that in arterial blood [40]. In the nonstimulated, innervated kidney (that is, with basal prevailing ERSNA) in the dog [41, 42] and human [43], the renal vein plasma norepinephrine concentration is the same as, or only slightly greater than, that in arterial blood. With graded electrical stimulation of the renal nerves over the frequency range of 0.5 to 18 Hz, however, both the renal venoarterial plasma norepinephrine concentration difference and the renal norepinephrine secretion rate increase in a frequency-dependent fashion [40, 41]. Similar findings have been observed with baroreflex alterations in ERSNA in the rat [44]. Thus, the consistently increased norepinephrine concen-

tration difference between the renal vein and artery supports the view that ERSNA is increased in patients with cirrhosis complicated by ascites and edema. Further support for this view comes from recent studies by Esler who, using radioisotope methods, showed that both total norepinephrine release to plasma (1141 ± 249 ng/min vs. 399 ± 33 ng/min) and renal norepinephrine release (305 ± 125 ng/min vs. 77 ± 13 ng/min) were increased in decompensated cirrhotic patients as compared to healthy volunteers [45].

Studies by Gatta and colleagues provide further evidence of increased ERSNA causing renal vasoconstriction in patients with liver cirrhosis and portal hypertension [46]. Measuring renal blood flow with the radioactive xenon washout technique, these investigators showed that an injection of dihydroergocristine, an alpha-adrenoreceptor antagonist, into the renal artery increased mean renal blood flow from 1.52 ± 0.30 to 1.73 ± 0.32 ml/min/g (normal value in 14 control subjects, 4.53 ± 0.97 ml/min/g) without altering arterial pressure. Thus, administration of an alpha-adrenoreceptor antagonist into the renal artery increased renal blood flow and decreased renal vascular resistance; that is, it produced renal vasodilation. These were acute studies and only small, insignificant increases in urinary flow rate and sodium and chloride excretion were observed, possibly because of a 13% decrease in inulin clearance.

Similar observations supporting the view that an increased ERSNA contributes to the renal vasoconstriction of decompensated liver cirrhosis were made by Ring-Larsen, Henriksen, and Christensen [47]. Six control subjects had mean renal blood flow (measured by the radioactive xenon washout technique) greater than 3.0 ml/min/g and peripheral plasma norepinephrine concentrations less than 0.3 ng/ml, whereas 24 patients with cirrhosis, ascites, and edema had values for mean renal blood flow between 1.0 and 3.0 ml/min/g and peripheral plasma norepinephrine concentrations between 0.2 and 2.0 ng/ml. The level of mean renal blood flow correlated inversely with the peripheral plasma norepinephrine concentration in the patients with decompensated cirrhosis whether or not the data on the control subjects were included. Bichet, Van Putten, and Schrier studied the response to an acute oral water load in 26 patients with decompensated liver cirrhosis and found a higher peripheral plasma norepinephrine concentration in the patients who excreted the water load abnormally than in those who excreted the load normally [48]. The authors noted (*1*) a positive correlation between plasma levels of norepinephrine and arginine vasopressin after the water load; (*2*) a negative correlation between plasma norepinephrine and the percentage of the water load excreted; (*3*) a positive correlation between plasma norepinephrine and both plasma renin activity and plasma aldosterone; (*4*) a negative correlation between plasma norepinephrine and urinary sodium excretion after the water load. The authors interpreted these data as indicating that increased sympathetic efferent discharge, based on the underfilling theory and reflected by peripheral plasma norepinephrine concentration, correlates closely with sodium and water retention in patients with decompensated liver cirrhosis, and that this increase might be of pathogenetic significance.

To study the effect of increased ERSNA on renal sodium retention, investigators have taken advantage of the technique of head-out water immersion as a physiologic state in which blood volume is redistributed and central blood volume is persistently increased [49]. The natriuretic and kaliuretic response is similar in the immersed individual to that observed after administration of an isotonic saline load of 2 liters over 2 hours. Water immersion provides a unique opportunity for testing the underfilling theory because it increases effective blood volume in the central or intrathoracic compartment without increasing total blood volume by potentially hazardous fluid administration, and it would be expected to be sensed by the left atrial mechanoreceptor as an increase in left atrial pressure [49].

Patients with decompensated liver cirrhosis have been subjected to head-out water immersion [50]. Striking natriuresis and kaliuresis result, often greater than that in control subjects; these alterations are independent of changes in the renin-angiotensin-aldosterone system and are accompanied by increases in urinary excretion of prostaglandin E_2. Because the usual antinatriuresis of the cirrhotic patient was reversed by a maneuver that redistributes blood volume without increasing total blood volume, these studies strongly support the concept that a decreased effective blood volume (a central tenet of the underfilling theory) is an important determinant of the avid renal sodium retention in patients with decompensated cirrhosis. In 8 patients with decompensated liver cirrhosis, Bichet, Groves, and Schrier showed that head-out water immersion increased cardiac index, right atrial pressure, and pulmonary capillary wedge pressure [51]. The peripheral plasma concentrations of renin, arginine vasopressin, aldosterone, and norepinephrine all were significantly decreased by immersion, and the patient's ability to excrete water and sodium after an acute oral water load improved significantly. The increase in right atrial pressure correlated positively with both the increase in the percentage of water load excreted (negatively correlated with the decrease in arginine vasopressin levels) and the increase in fractional sodium excretion. The decrease in plasma norepinephrine concentration produced by head-out water immersion was correlated with the concurrent increase in right atrial pressure. There was an inverse correlation between plasma norepinephrine concentration and fractional sodium excretion. Thus, if one assumes that the increase in right atrial pressure is associated with a directionally similar change in left atrial pressure, the increased central blood volume induced by immersion might stimulate left atrial mechanoreceptors and produce decreases in arginine vasopressin and ERSNA. The decrease in ERSNA in turn could contribute to reductions in plasma concentrations of renin, aldosterone, and norepinephrine. The net result would be an increase in the kidney's ability to excrete a sodium and water load.

Epstein performed similar studies of water immersion in 15 patients with decompensated cirrhosis and found that whereas 13 of the 15 patients had a natriuresis, only 6 of the 15 had a suppression of the elevated peripheral plasma norepinephrine concentration [52]. Neither the peak diuretic nor the peak natriuretic response to immersion correlated with basal plasma norepinephrine concentration or with the extent of suppression of plasma norepinephrine concentration. Because of the relative fallibility of assessing ERSNA from measurements of peripheral plasma norepinephrine concentration [37–39], measurement of the renal venoarterial plasma norepinephrine concentration difference during water immersion will be needed to define more precisely the role of increased ERSNA in the renal

sodium and water retention of decompensated cirrhosis.

The role of the renal nerves in the renal sodium retention of cirrhosis has been studied in several experimental models. In acute experiments, the antinatriuretic response to a hepatic venous outflow block (produced by infusion of histamine into the portal vein) was not affected by renal denervation [53]. Using the model of biliary cirrhosis produced by chronic ligation of the bile duct, Chaimovitz and colleagues reported that neither acute unilateral surgical denervation of the kidney nor renal arterial infusion of phenoxybenzamine altered urinary sodium excretion in anesthetized dogs [54]. It is unclear, however, whether these animals had developed ascites or even renal sodium retention, as their fractional sodium excretion ranged from 0.12% to 0.24%, as compared to an average of 0.34% in similarly prepared normal control animals. Furthermore, in dogs with common bile duct ligations, the interventions did produce significant increments in urinary sodium excretion in the experimental kidneys as compared to the contralateral control kidneys but the urinary sodium excretion responses were not greater than those in the normal control animals. The animals might have been studied too early, prior to activation of the neural reflex arcs that could lead to ERSNA as a mediator of renal sodium retention. Alternately, the experimental model of biliary cirrhosis might not be accompanied by so marked a tendency to renal sodium retention. In support of the view that experimental biliary cirrhosis may not be representative of other forms of cirrhosis, Chaimovitz and colleagues assessed the natriuretic and diuretic responses to extracellular fluid volume expansion in patients with primary biliary cirrhosis; they demonstrated that both the diuretic and natriuretic responses were greater than those observed in normal volunteers and edema-free patients with alcoholic cirrhosis [55].

Pathogenesis of the hepatorenal syndrome

The hepatorenal syndrome can be defined as renal failure in patients with liver disease in the absence of clinical, laboratory, or anatomic evidence of other known causes of renal failure [2]. The clinical diagnostic criteria can be considered in two categories, general and renal. The general criteria are: (*1*) presence of liver disease; (*2*) absence of primary renal disease or other known causes of renal failure; (*3*) acute or subacute onset of progressive renal functional impairment; and (*4*) no sustained improvement with expansion of effective blood volume [2]. The renal functional criteria are: (*1*) reduced glomerular filtration rate; (*2*) urine sodium concentration less than 10 mEq/liter; (*3*) fractional sodium excretion less than 1%; and (*4*) ratio of urine to plasma osmolality (U/Posm) greater than 1 [2].

No known clinical, functional, or laboratory characteristics (or combination thereof) identify the patients with decompensated cirrhosis who will develop the hepatorenal syndrome. As summarized by Papper, the largest body of evidence still supports the view that a renal circulatory mechanism is the root cause of the hepatorenal syndrome [2]. The combination of reduced glomerular filtration rate, concentrated urine, and very low urinary sodium concentration is characteristic of a reduction in renal perfusion, and, in fact, measured renal blood flow is reduced [56, 57]. The slight reduction in mean arterial pressure that is characteristically present and the frequency with which the onset of renal failure follows clinical events that reduce effective blood volume (gastrointestinal bleeding, paracentesis, diuresis) support the importance of an alteration in the renal circulation. Attempts to restore effective blood volume and renal perfusion may improve renal function transiently [56]. The relative renal cortical ischemia and unstable renal arterial circulation (afferent renal arterial vasoconstriction) are evidence for abnormal renal circulation in humans with hepatorenal syndrome [34].

Kidneys from patients with the hepatorenal syndrome function normally in the presence of a normal liver. Relieving the kidney of the burden of an abnormal liver has been accomplished both by successfully transplanting the kidney from a patient with the hepatorenal syndrome into a noncirrhotic recipient [3] and by transplanting a normal liver into a patient with the hepatorenal syndrome [58]. These findings prove that the renal failure in hepatorenal syndrome is functional in nature, representing a response to extrarenal influences rather than an intrinsic renal disorder.

The extrarenal circulation of patients with the hepatorenal syndrome is also abnormal. Although cardiac output and plasma volume are variably affected, cerebral and hepatic blood flow, like renal blood flow, are reduced [59, 60]. When cardiac output is elevated, peripheral vasodilation occurs, with arteriovenous shunting of blood in muscles, lung, and possibly in the kidney and liver [61].

The observations that the renal failure of hepatorenal syndrome is functional and, under certain circumstances, reversible and that it occurs in the setting of an abnormal renal and extrarenal circulation suggests that the abnormal renal circulation represents the kidney's physiologic response to alterations in the extrarenal circulation. In keeping with this view, both the underfilling and overflow theories predict disturbances in the neural control of effective blood volume and in the extrarenal circulation; these disturbances elicit increases in ERSNA that are capable of causing the abnormalities found in the renal circulation: afferent renal arterial vasoconstriction, relative renal cortical ischemia, and unstable renal arterial circulation. Furthermore, as cited earlier, there is increasing evidence for increased ERSNA in decompensated cirrhotic patients.

An alternate view is that a humoral or neurohumoral agent, produced or inadequately inactivated by the diseased liver or shunted away from the liver via portal-systemic anastomoses, is responsible for both the abnormal renal and extrarenal circulation. Many humoral agents have been considered: vasodilator material, jaundiced serum, false neurotransmitters, endotoxins, renin-angiotensin, prostaglandins, vasoactive intestinal polypeptide, and kallikrein-kinin. Although improvements in renal function in the hepatorenal syndrome correlated with decreases in peripheral plasma renin activity following peritoneovenous shunting [62], saralasin, a competitive antagonist of angiotensin II, failed to improve renal function in patients with hepatorenal syndrome [63].

As recently summarized by Epstein and Lifschitz [64], some diseases are characterized by decreased effective blood volume and avid renal sodium retention; decompensated cirrhosis clearly falls in this category [65]. Administration of prostaglandin synthesis inhibitors to patients with such a disease can elicit marked reduction in glomerular filtration rate and thus produce acute renal failure. Studying dogs with experimental biliary cirrhosis and ascites produced by common bile duct ligation,

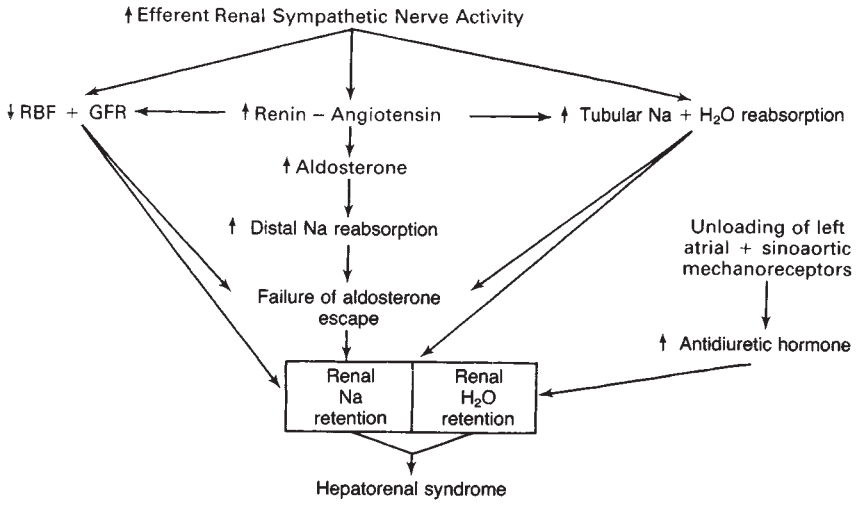

Fig. 7. *Pathways contributing to the pathogenesis of the hepatorenal syndrome.*

Zambraski and Dunn found that indomethacin produced marked renal vasoconstriction and decreased glomerular filtration rate [66]. Thus, heightened renal prostaglandin synthesis might be an important renal adaptive mechanism in states of reduced effective blood volume, and defects in this response could contribute to the renal hemodynamic abnormalities observed in the hepatorenal syndrome. Additionally, decreased plasma concentration of prekallikrein and bradykinin, peptides with renal vasodilatory capacity, have been observed in the hepatorenal syndrome [67].

Of more recent interest is the discovery of an atrial natriuretic factor, a small-molecular-weight peptide derived from specific granules within atrial but not ventricular muscle cells [68]. This factor possesses diuretic and natriuretic properties but does not inhibit sodium-potassium ATPase activity nor does it cross-react with digoxin antibody. Mechanisms governing its release are not clearly known, but it might be regulated by alterations in left atrial pressure that reflect changes in blood volume (the underfilling theory) or by reflex alterations in cardiopulmonary sympathetic nerve activity that reflect intrahepatic mechanoreceptor stimulation (the overflow theory). Whether decreased circulating levels of atrial natriuretic factor also contribute to the renal sodium retention of decompensated cirrhosis is not known. A detailed review of the available information concluded that there is insufficient evidence supporting the view that a humoral agent is solely responsible for both the abnormal renal and extrarenal circulation in the hepatorenal syndrome [2].

In the overall pathogenesis of the hepatorenal syndrome, it is my view that increased ERSNA interacts with a variety of hemodynamic and humoral abnormalities to produce the renal failure (Fig. 7). But because increased ERSNA alone can directly elicit virtually all the postulated hemodynamic, humoral, and tubular mechanisms proposed to explain the clinical manifestations of the hepatorenal syndrome, it seems reasonable to place primary emphasis on this phenomenon.

In evaluating a patient suspected of having the hepatorenal syndrome, it is essential that one exclude the presence of volume depletion. A sustained improvement (for example, diuresis and increase in glomerular filtration rate) with expansion of effective blood volume would be evidence against hepatorenal syndrome and in favor of reversible (prerenal) azotemia and oliguria secondary to decreased effective blood volume. When volume repletion does not produce improvement in renal function, and when other known causes of renal failure are absent, the diagnosis of hepatorenal syndrome becomes more secure.

The treatment of established hepatorenal syndrome is generally unsatisfactory [2]. The introduction of a peritoneovenous (La Veen) shunt for the continuous return of ascitic fluid to the circulation has an uncertain role clinically but has provided additional insight into the pathogenesis of the hepatorenal syndrome. Some [69–70] but not all [71] investigators have observed a decrease in intrahepatic sinusoidal pressure following peritoneovenous shunting, as reflected by measurements of wedged hepatic vein pressure. In patients with well-documented hepatorenal syndrome, insertion of a peritoneovenous shunt or construction of a side-to-side portacaval shunt can result in significant increases in glomerular filtration rate and plasma volume with spontaneous diuresis and natriuresis [62, 72]. That these two dissimilar procedures appear to have a common effect suggests that both translocate fluid from the splanchnic area to the venous circulation and preferentially expand the central blood volume compartment. Nevertheless, the peritoneovenous shunt cannot be recommended in the routine management of cirrhotic patients with ascites or the hepatorenal syndrome until unambiguous demonstration of its therapeutic efficacy is available from randomized, prospective clinical trials [73, 74].

Questions and answers

DR. SERAFINO GARELLA (*Renal Division, Michael Reese Hospital*): How do you relate your thesis concerning sodium retention to the fall in GFR that is such an important part of the hepatorenal syndrome?

DR. DIBONA: It would be reasonable to conjecture that the renal insufficiency is related to sustained and progressively intense renal nerve stimulation. I rather think that it is not the sole factor and that there must be a concomitant failure of previously effective compensatory mechanisms. For example, we know of the deleterious effect on GFR when indomethacin

or other prostaglandin synthesis inhibitors are administered to cirrhotic patients who have sodium retention and edema formation [64–66]. It is reasoned that renal prostaglandin synthesis increases as a compensatory mechanism to maintain GFR and renal blood flow and to oppose the collective influence of several renal vasoconstrictor stimuli (for example, nerve activity, angiotensin II). In the hepatorenal syndrome, the precise nature of the compensatory mechanisms and the reasons for their eventual failure are unknown.

DR. FREDRIC COE (*Renal Section, Billings Hospital*): It seems from what you have said that prazosin and propranolol given together ought to be extremely effective in treating cirrhotic patients who have low GFRs and sodium retention. Has this combination been tried?

DR. DIBONA: I do not know the results of combined prazosin and propranolol administration to such cirrhotic patients. An important issue would be the avoidance of a substantial reduction in arterial pressure that might attenuate any natriuretic responses to the combined therapy.

DR. COE: Do you think the hepatic mechanoreceptor mechanism plays a role in the very marked sodium and water retention that occurs in congestive heart failure with passive congestion of the liver?

DR. DIBONA: It is possible that congestive heart failure with passive hepatic congestion would increase intrahepatic sinusoidal pressure sufficiently, as with constriction of the thoracic inferior vena cava above the diaphragm [25], and lead to a similar reflex increase in efferent renal sympathetic nerve activity.

DR. JORDAN J. COHEN: Data from water immersion studies indicate that a prompt increase in hemodynamics leads to a natriuresis in patients with cirrhosis. This observation puzzles me. It would seem to suggest that the underlying sodium-retaining mechanism can be overridden by volume expansion and that the potential exists for "escape" from the sodium-retaining effects of the renal nerve stimulation. Why doesn't that happen spontaneously? If renal nerve stimulation promotes sodium retention, why doesn't it expand intravascular volume and eventually produce the kind of effect that water immersion does?

DR. DIBONA: The answer may lie in differences in kinetics and time course. Head-out water immersion produces an acute, substantial and preferential increase in intrathoracic (central) blood volume. The renal sodium retention from chronic renal nerve stimulation is slower, probably smaller on a daily basis, and is more generally distributed in accord with the forces governing the abnormal blood volume distribution in cirrhosis. Therefore, it is possible that the renal sodium retention due to chronic renal nerve stimulation might not produce the same stimulus, in terms of intrathoracic blood volume expansion, as does head-out water immersion.

DR. GARY TOBACK (*Renal Section, Billings Hospital*): Some believe that the bile acids that accumulate in the plasma in patients with end-stage liver disease, especially in the presence of renal ischemia, might affect the kidney by diminishing renal hemodynamics. Is this an important factor?

DR. DIBONA: Perfusion of an isolated rabbit kidney with plasma taken from baboons with surgically induced obstructive jaundice increases the renal vasoconstrictor response to norepinephrine [75]. In rats with only unconjugated hyperbilirubinemia, no difference was found in the incidence of ischemia-induced renal impairment between animals with and those without bile duct ligation [76], whereas rats with bile duct ligation and conjugated hyperbilirubinemia had an increased incidence of renal failure [77]. These findings suggest that increased levels of conjugated bilirubin render the kidney more susceptible to ischemia. However, clinical observations indicate that the hepatorenal syndrome can develop while jaundice is decreasing or in the presence of minimal jaundice [2].

DR. TOBACK: The data you presented indicate that volume expansion leads to an increase in sodium clearance in patients with biliary cirrhosis (compared to controls), whereas in Laennec's cirrhosis sodium clearance is reduced. Does this imply that different types of cirrhosis result in different mechanisms for renal sodium retention?

DR. DIBONA: Portal hypertension (increased intrahepatic sinusoidal pressure) is related to nodular regeneration in the liver and to cirrhosis. Nodular regeneration is generally considered a late feature of primary biliary cirrhosis; it is therefore possible that the development of increased intrahepatic sinusoidal pressure as the initial step in both the underfilling and overflow theories is more gradual in primary biliary cirrhosis than in Laennec's cirrhosis. This could account for some of the differences observed in renal sodium handling.

DR. DAVID BUSHINSKY (*Renal Section, Billings Hospital*): Another therapeutic approach suggested by your thesis would be to infuse a pressor agent such as dopamine to increase renal blood flow and then produce neuronal blockade with an agent such as guanethidine. Given the fact that the hepatorenal syndrome is associated with virtually a 100% mortality rate, would such an approach be reasonable?

DR. DIBONA: One would anticipate that an improvement in renal perfusion coupled with a reduction in the postulated increased level of renal nerve activity would be beneficial. Two groups of workers have used octapressin to increase renal blood flow and decrease renal vascular resistance in cirrhotic patients [78, 79]. In considering such therapy, it is important that one avoid maneuvers that would decrease renal arterial pressure and thus attenuate any beneficial effects derived from improved renal perfusion.

DR. COHEN: Do we know how renal nerve stimulation actually translates into increased tubular sodium transport? What is the molecular basis for the effect?

DR. DIBONA: The neurotransmitter released from renal nerve terminals, norepinephrine, stimulates Na-K-ATPase; it produces this effect by counteracting the inhibitory effect of endogenous vanadate on the enzyme [80, 81]. Therefore increased norepinephrine release during renal nerve stimulation would increase the activity of the Na-K-ATPase pump at the basolateral membrane of the renal tubular epithelial cell.

DR. SATISH KATHPALIA (*Renal Division, Michael Reese Hospital*): Do kidneys transplanted from cirrhotic patients begin to function because of denervation?

DR. DIBONA: The evidence would indicate that the abnormal renal function is reversed by changing the hepatic environment, either by transplanting the kidney into a recipient with a normal liver [3] or by transplanting a normal liver into the patient [58].

DR. COHEN: What is the anion composition of urine when one produces a saluresis by interrupting renal nerve traffic?

DR. DIBONA: The predominant anion is chloride.

DR. BRIAN DUFFY (*Attending Nephrologist, Michael Reese Hospital*): In the clinical setting, many of the precipitating causes of hepatorenal syndrome also cause volume depletion. Does this relate to a sudden burst of renal nerve activity? And why is it that the syndrome seems only to develop in the hospital? Rarely does a patient enter the hospital with established hepatorenal syndrome.

DR. DIBONA: It is reasonable to predict that maneuvers producing intravascular volume depletion will increase the stimuli (underfilling hypothesis) and further acutely increase efferent renal sympathetic nerve activity. The propensity for the hepatorenal syndrome to develop in the hospital possibly relates to the fact that many of the precipitating events (vigorous diuresis, overzealous paracentesis, bleeding, hypotension) occur in hospital.

DR. SUSAN FELLNER (*Renal Section, Billings Hospital*): Is it possible in the experimental situation to surgically interrupt the hepatic afferents to examine the contribution of the liver itself in contrast to that stemming from the reduced effective blood volume?

DR. DIBONA: This question can be pursued in experimental hepatic cirrhosis produced by common bile duct ligation. Hepatic afferent nerves course along the hepatic artery, the portal vein, and possibly other structures [25]. An important but difficult consideration is assessing the completeness of hepatic denervation.

DR. STEPHEN GLUCK (*Renal Section, Billings Hospital*): Have you examined whether the effects you ascribe to abnormalities in renal nerve function in the hepatorenal syndrome and other diseases could be due to changes in the number of renal alpha or beta receptors?

DR. DIBONA: The mammalian kidney contains alpha and beta adrenoreceptors that are variously distributed on glomeruli, vessels, and tubules. Renal hypertension or hypertension due to DOCA and NaCl administration in rats does not alter the renal alpha- or beta-adrenoreceptor concentration or binding affinity [82, 83]. Abnormalities in renal alpha-1 and alpha-2 adrenoreceptor concentration (but not binding affinities) have been described in the spontaneously hypertensive rat and the Dahl salt-sensitive rat [83].

DR. GARELLA: Many clinical reports claim that sodium retention in cirrhotic patients can be alleviated by peritoneovenous (La Veen) shunt. Doesn't this observation argue against a specific hepatorenal reflex?

DR. DIBONA: Although the peritoneovenous shunt repeatedly has been demonstrated to induce a diuresis and a natriuresis, most observers have noted that insertion of the shunt was insufficient to sustain a diuresis and natriuresis and that concomitant diuretic therapy was required to maintain a therapeutic response [73]. If the shunt can replete a diminished effective blood volume, these observations suggest the possibility of additional mechanisms, unrelated to the underfilling hypothesis, that are involved in the renal sodium retention. In addition, the shunt would not correct the abnormality responsible for the increase in intrahepatic sinusoidal pressure and, by increasing effective blood volume, actually might increase it.

DR. ALAN HALLINE (*Medical Resident, Michael Reese Hospital*): Is there any information relating renal nerve function to prostaglandin production? Are prostaglandins efficacious in the hepatorenal syndrome?

DR. DIBONA: Renal nerve stimulation at intensities that do not affect renal blood flow or produce marked renal vasoconstriction cause increased renal prostaglandin E_2 secretion [6]. In view of the role of prostaglandins as locally active substances, it might be preferable to seek ways of increasing renal prostaglandin synthesis. Prostaglandins have been given to a limited number of patients with the hepatorenal syndrome. Administration of prostaglandin E_1 in 3 patients over 1 hour failed to affect urine volume or sodium excretion despite two- to tenfold increases in plasma prostaglandin E concentrations [84].

DR. DIMITRIOS EMMANOUEL (*Renal Section, Billings Hospital, Chicago*): Has anyone ever described a patient with Shy-Drager syndrome who developed cirrhosis? Such an experiment of nature would be an interesting test of your thesis.

DR. DIBONA: I am unaware of any reports concerning patients with Shy-Drager syndrome who developed cirrhosis.

DR. COHEN: How do you manage patients with the hepatorenal syndrome?

DR. DIBONA: The patient presented today illustrates my general approach to the clinical management of hepatorenal syndrome. I believe it is important to exclude reversible volume depletion by cautious intravascular volume expansion under central cardiovascular pressure monitoring. Given the extraordinarily high mortality rate in established hepatorenal syndrome, it is not surprising that physicians have tried a wide variety of treatments [2]. While these have been generally unsuccessful, the dismal natural history of hepatorenal syndrome justifies continued rigorous trials of newer forms of therapy, including peritoneovenous shunting [73, 74].

DR. COE: It is my understanding that the hepatorenal syndrome can be divided into two components. The first is renal sodium retention, which can become extremely severe and can make the patient miserable because of ascites. The second is the fall in GFR. It has been my impression that the impact of a fall in GFR and renal failure on mortality is not as great as is the effect of the underlying liver disease. The latter seems to be the limiting factor in determining the ultimate clinical outcome. Is it your feeling that if one could correct the low GFR—by pharmacologic means or otherwise—that survival would be lengthened?

DR. DIBONA: The evidence from the clinical transplantation experience is that the abnormality in hepatic function is the major determinant of overall mortality [3, 58]. However, to the extent that the decrease in GFR and accompanying hyperkalemia and uremic syndrome accelerate the clinical course and decrease the time available for spontaneous improvement in hepatic function or for hepatic transplantation, a therapeutic intervention restoring GFR toward normal would appear to be beneficial.

DR. FELLNER: It is a common observation that patients often enter the hospital with reasonable baseline liver and kidney function only to experience parallel hepatic and renal failure. Is it possible that the neural and humoral factors that contribute to renal ischemia and the fall in GFR also contribute to a fall in hepatic function by decreasing hepatic blood flow? In other words, are we seeing the added effects of hepatic ischemia superimposed on a scarred liver?

DR. DIBONA: Hepatic blood flow is decreased in cirrhosis and is subject to the same neurohumoral influences that affect the general circulation. However, because alterations in sympa-

thetic neural outflow to vascular beds is differentiated, we cannot assume that alterations in efferent renal sympathetic nerve activity are associated with parallel changes in sympathetic neural outflow to the hepatic vascular bed.

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Note added in proof

Further evidence of enhanced renal sympathetic nerve activity in decompensated cirrhotic patients has been provided by Henriksen et al (Henriksen JH, Ring-Larsen H, Kanstrup I-L, Christensen NJ: Splanchnic and renal elimination and release of catecholamines in cirrhosis. Evidence of enhanced sympathetic nervous activity in patients with decompensated cirrhosis. *Gut* in press, 1984).

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